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(19) (CA) **APPLICATION FOR CANADIAN PATENT** (12)

(54) Anti-Viral Aromatic O-Alkylated Oximes, Esters and Thioethers

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(71) Uniroyal Chemical Ltd./Uniroyal Chemical Ltée - Canada ;

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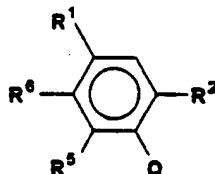
(57) 20 Claims

Notice: This application is as filed and may therefore contain an incomplete specification.



ABSTRACT

Compounds of the formula



wherein Q is -C=NOR^4 or -XR^4 ;



X is oxygen or sulphur;

R¹ is hydrogen, halogen, C₁-C₄ alkyl or C₁-C₄ alkoxy;

R² is hydrogen, halogen, C₁-C₄ alkyl, C₁-C₄ alkoxy, C₃-C₄ alkenyloxy, C₃-C₄ alkynyloxy, mono-, di- or tri-halomethyl, trifluoromethoxy, C₁-C₄ alkylthio, C₃-C₄ branched alkylthio, nitro, or cyano;

R³ is hydrogen or C₁-C₄ alkyl;

R⁴ is C₃-C₆ alkenyl, C₃-C₆ alkynyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxyalkyl, C₁-C₆ alkylthioalkyl, C₁-C₆ hydroxyalkyl, C₁-C₆ acyloxyalkyl, C₁-C₆ aryloxyalkyl, C₁-C₆ carboxyalkyl, C₁-C₆ alkylcarboxyalkyl, C₆-C₁₂ arylcarboxyalkyl, C₁-C₆ aminoalkyl, C₁-C₆ alkylaminoalkyl, C₁-C₆ dialkylaminoalkyl, C₁-C₆ trialkylsilylalkyl, wherein each of the aforementioned alkyl moieties may be straight-chain or branched; C₃-C₆ cycloalkyl, C₁-C₆ alkylphenyl, C₇-C₁₂ arylalkyl, C₇-C₁₂ alkarylalkyl, or heterocyclalkyl, wherein the heterocyclic moiety is morpholinyl, piperidinyl, pyrrolidinyl, piperazinyl, oxiranyl, oxetanyl, furanyl, tetrahydropyranyl or tetrahydrofuranyl;

R' is C₁-C₆ haloalkyl, C₁-C₆ alkoxyalkyl, C₁-C₆ alkylthioalkyl, C₁-C₆ hydroxyalkyl, C₁-C₆ acyloxyalkyl, C₁-C₆ aryloxyalkyl, C₁-C₆ aminoalkyl, C₁-C₆ alkylaminoalkyl, C₁-C₆ dialkylaminoalkyl, C₁-C₆ trialkylsilylalkyl, where in each of the aforementioned

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alkyl moieties may be straight-chain or branched; C₁-C₆ alkylphenyl, C₇-C₁₂ arylalkyl, C₇-C₁₂ alkarylalkyl, or heterocyclalkyl, wherein the heterocyclic moiety is morpholinyl, piperidinyl, pyrrolidinyl, piperazinyl, oxiranyl, oxetanyl, furanyl, tetrahydropyranyl or tetrahydrofuranyl;

R⁵ is hydrogen, halo, methyl, mono-, di- or tri-halomethyl; and

R⁶ is an aliphatic or cyclic side chain as defined herein.

These compounds are useful for inhibiting the growth or replication of retroviruses such as HIV.

ANTI-VIRAL AROMATIC O-ALKYLATED OXIMES,
ETHERS AND THIOETHERS

5 Field of the Invention

 This invention relates to novel aromatic O-alkylated
oximes, ethers and thioethers. In particular, this
invention relates to novel aromatic O-alkylated oximes,
10 ethers and thioethers useful as anti-viral agents. More
particularly, this invention relates to novel aromatic O-
alkylated oximes, ethers and thioethers useful as agents
against certain retroviruses such as the members of the
group of Human Immunodeficiency Viruses (HIV).

15

Background of the Invention

 Retroviruses are viruses whose replication requires
the transcription of viral RNA into DNA using the viral
reverse transcriptase molecules attached to the viral
20 RNA. This reverse transcription is the opposite of
normal transcription which makes RNA from DNA.

 Known retroviruses include HIV-1, HIV-2, the herpes
family of viruses, HTLV-1 and cytomegalovirus (CMV).
25 HIV, the virus which is presently believed to cause
acquired immunodeficiency syndrome (AIDS), is considered
one of the principle threats to human life and health
worldwide.

 Various anti-HIV compounds have been proposed as
30 useful in the treatment and prevention of AIDS, e.g.,
zidovudine (AZT), didanosine (ddI), zalcitabine (ddC),
nevirapine, and dextran sulfate. However, none of the
proposed compounds have been proven to be totally
effective in the treatment or prevention of AIDS. For
35 example, the three currently FDA approved compounds for
the treatment of AIDS, i.e., AZT, ddI and ddC, can all
cause undesirable side effects in a patient, such as
inhibition of bone marrow cell growth, and their
effectiveness is limited by virus mutation.

40 U.S. Patent No. 5,268,389 describes certain

thiocarboxylate ester compounds useful for inhibiting the growth or replication of HIV.

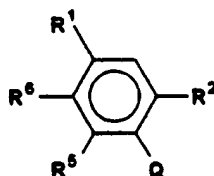
It is the purpose of this invention to provide novel aromatic O-alkylated oximes, ethers and thioethers, useful as anti-viral agents.

It is also the purpose of this invention to provide a method for inhibiting or preventing the growth or replication of human immunodeficiency viruses using the novel aromatic O-alkylated oximes, ethers and thioethers.

Finally, it is also the purpose of this invention to provide compositions useful for inhibiting or preventing the growth or replication of human immunodeficiency viruses, comprising the novel aromatic O-alkylated oximes, ethers and thioethers.

Description of the Invention

This invention relates to a compound of the formula



(I)

wherein Q is -C-NOR^4 or -XR^1 ;



X is oxygen or sulphur;

R¹ is hydrogen, halogen, C₁-C₄ alkyl or C₁-C₄ alkoxy;

R² is hydrogen, halogen, C₁-C₄ alkyl, C₁-C₄ alkoxy, C₁-C₄ alkenyloxy, C₁-C₄ alkynyloxy, mono-, di- or tri-halomethyl, trifluoromethoxy, C₁-C₄ alkylthio, C₁-C₄ branched alkylthio, nitro, or cyano;

R³ is hydrogen or C₁-C₄ alkyl;

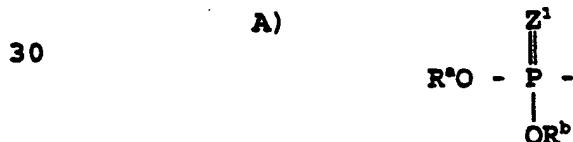
R^4 is C_1-C_6 alkenyl, C_3-C_6 alkynyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxyalkyl, C_1-C_6 alkylthioalkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 acyloxyalkyl, C_1-C_6 aroyloxyalkyl, C_1-C_6 carboxyalkyl, C_1-C_6 alkylcarboxyalkyl, C_6-C_{12} arylcarboxyalkyl, C_1-C_6 aminoalkyl, C_1-C_6 alkylaminoalkyl, C_1-C_6 dialkylaminoalkyl, C_1-C_6 trialkylsilylalkyl, wherein each of the
 5 aforementioned alkyl moieties may be straight-chain or branched; C_3-C_6 cycloalkyl, C_1-C_6 alkylphenyl, C_7-C_{12} arylalkyl, C_7-C_{12} alkarylalkyl, or heterocyclalkyl, wherein the heterocyclic moiety is morpholinyl,
 10 piperidinyl, pyrrolidinyl, piperazinyl, oxiranyl, oxetanyl, furanyl, tetrahydropyranyl or tetrahydrofuranyl;

R' is C_1-C_6 haloalkyl, C_1-C_6 alkoxyalkyl, C_1-C_6 alkylthioalkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 acyloxyalkyl, C_1-C_6 aroyloxyalkyl, C_1-C_6 aminoalkyl, C_1-C_6 alkylaminoalkyl, C_1-C_6 dialkylaminoalkyl, C_1-C_6 trialkylsilylalkyl, wherein each of the aforementioned
 15 alkyl moieties may be straight-chain or branched; C_1-C_6 alkylphenyl, C_7-C_{12} arylalkyl, C_7-C_{12} alkarylalkyl, or heterocyclalkyl, wherein the heterocyclic moiety is morpholinyl, piperidinyl, pyrrolidinyl, piperazinyl, oxiranyl, oxetanyl, furanyl, tetrahydropyranyl or tetrahydrofuranyl;

R^5 is hydrogen, halo, methyl, mono-, di- or tri-halomethyl;

R^6 is

1) $R^2 - NH -$, wherein R^2 is



35 wherein R^a and R^b are independently hydrogen or C_1-C_6 alkyl; and Z^1 is O or S; r



wherein Z^2 is O or S; and

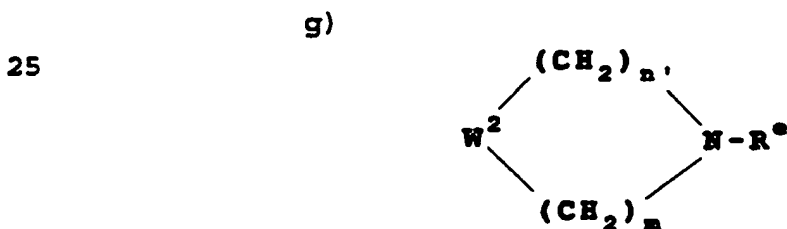
R^{A} is:

- 5 a) fully unsaturated, partially or fully reduced or substituted oxathiinyl, furanyl, dithiinyl, dioxinyl, thienyl, thiazolyl, oxazolyl, isoxazolyl, 10 isothiazolyl, thiadiazolyl, pyrazolyl, pyrrolyl, imidazolyl, pyranyl, oxathiazinyl, oxadiazolyl, or indolyl;
- 15 b) substituted or unsubstituted, linear or branched $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_2\text{-C}_6$ alkenyl, $\text{C}_2\text{-C}_6$ alkynyl, $\text{C}_1\text{-C}_6$ alkoxy, $\text{C}_2\text{-C}_6$ alkenyloxy, $\text{C}_2\text{-C}_6$ alkynloxy, or $\text{C}_1\text{-C}_6$ mono- or di-alkylamino; $\text{C}_3\text{-C}_6$ cycloalkyl, $\text{C}_3\text{-C}_6$ cycloalkyl $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_3\text{-C}_6$ cycloalkenyl, 20 unsubstituted or substituted by $\text{C}_1\text{-C}_6$ alkyl or $\text{C}_7\text{-C}_6$ phenylalkyl; or
- 25 c) aryl, aralkyl, aryloxyalkyl, or cycloalkylaryloxy wherein each alkyl moiety contains from 1 to 10 carbon atoms and each aryl moiety is naphthyl, phenyl or phenyl substituted by one or more halo, $\text{C}_1\text{-C}_6$ alkyl, carboxyl, $\text{C}_1\text{-C}_6$ haloalkyl, $\text{C}_1\text{-C}_6$ alkylthio, phenyl, nitro, amino, $\text{C}_1\text{-C}_6$ 30 alkoxy-carbonylamino, hydroxyl, acetyl, acetyloxy, phenoxy, $\text{C}_1\text{-C}_6$ alkoxy-carbonyl or $\text{C}_1\text{-C}_6$ alkyl-carbonyl;
- 35 (d) $\text{R}^7 - \text{W} -$, wherein W is O, NH or NR^f wherein R^f is $\text{C}_1\text{-C}_6$ alkyl; and R^7 is linear or branch d, unsubstituted

5 or halo-substituted C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl C_1-C_6 alkyl, C_3-C_7 cycloalkenyl unsubstituted or substituted by C_1-C_6 alkyl, unsubstituted phenyl or phenyl substituted by halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, carboxyl, C_1-C_6 alkythio, phenyl, nitro, amino, hydroxyl, acetyl, acetyloxy, phenoxy, C_1-C_6 alkoxycarbonyl, or C_1-C_6 alkylcarbonyl;
 10 furanylalkyl, tetrahydrofuranylalkyl, oxetanylalkyl, or oxiranylalkyl;

e) $R^8 - W^1 - R^9$, wherein
 15 R^9 is a linear or a branched C_1-C_6 alkylidene;
 W^1 is O or S; and
 R^8 is linear or branched C_1-C_6 alkyl;

f) $R^9 R^{10} - N - R^9$, wherein
 20 R^9 is as defined above; and R^9 and R^{10} are independently linear or branched C_1-C_6 alkyl;



30

wherein

R^9 is as defined above;
 W^2 is O, S, NH, NR^{11} or $CR^{12}R^{13}$; wherein R^{11}
 35 is linear or branched C_1-C_6 alkyl; R^{12} and R^{13} are independently hydrogen or linear or branched C_1-C_6 alkyl; and

n' and m are independently 1, 2 or 3;

h) $R^{14}-O_2-C-R^e$, wherein

R^e is as defined above; and R^{14} is linear or branched C_1-C_6 alkyl, C_3-C_6 alkenyl, or C_3-C_6 alkynyl; or C_3-C_7 cycloalkyl, C_3-C_7 cycloalkyl C_1-C_6 alkyl, or C_3-C_7 cycloalkenyl, unsubstituted or substituted by C_1-C_6 alkyl;

i) $U-R^e-$, wherein

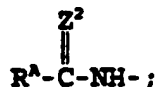
R^e is as defined above; U is hydroxyl, acyl oxy, aryloxy, arylsulphonyloxy, nitro, cyano or trimethylsilyl;

j) 1-adamantyl, 2-adamantyl or bornyl;

k) $Ar^1 - R^e -$, wherein

R^e is as defined above; and Ar^1 is phenyl or phenyl substituted independently with one to three halogen, mono-, di- or tri- halomethyl, nitro, C_1-C_4 alkyl, C_3-C_4 alkenyl, C_1-C_4 alkyloxy, C_3-C_4 alkenyloxy, or C_3-C_4 alkynyloxy.

Preferred compounds are those compounds wherein R^6 is



Z^2 is O or S; and

R^A is

a) fully unsaturated, partially or fully reduced or substituted oxathiinyl, furanyl, dithiinyl, dioxinyl, thienyl, thiazoyl, oxazoyl, isoxazoyl, isothiazoyl, thiadiazolyl, pyrazolyl, pyrrolyl, pyranyl, oxathiazinyl, or oxadiazolyl;

b) linear or branched C₁-C₈ alkyl, C₃-C₈ alkenyl, C₃-C₈ alkynyl, C₁-C₈ alkoxy, C₃-C₈ alkenyloxy, C₃-C₈ alkynloxy, or C₁-C₈ mono- or di- alkylamino; C₃-C₆ cycloalkyl or C₃-C₆ cycloalkenyl;

5 c) phenyl or phenyl substituted by one or more halo, C₁-C₈ alkyl, C₁-C₈ haloalkyl, C₁-C₈ alkylthio, phenyl, amino, hydroxyl, carboxyl, acetyl, acetyloxy, C₁-C₈ alkoxycarbonyl, C₁-C₈ alkylcarbonyl or phenoxy; C₇-C₈ phenylalkyl or C₇-C₈ phenoxyalkyl.

10 More preferred are those compounds wherein R^A is

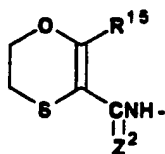
a) dihydro-3-oxathiinyl, furanyl, dihydrofuranyl, thienyl, pyrrolyl, dihydro-2-dithiinyl, or dihydro-2-dioxinyl, which can be substituted by one to three C₁-C₄ alkyl or C₁-C₄ alkoxyalkyl groups;

15 b) linear or branched C₁-C₈ alkyl, C₂-C₈ alkenyl, C₃-C₈ alkynyl, C₁-C₈ alkoxy, C₃-C₈ alkenyloxy, C₃-C₈ alkynyloxy or C₁-C₈ mono- or di-alkylamino; C₃-C₆ cycloalkyloxy or C₃-C₆ cycloalkenyloxy; or

20 c) phenyl or phenyl substituted by one or more halo, C₁-C₈ alkyl, C₁-C₈ haloalkyl, C₁-C₈ alkylthio, carboxyl, amino, C₁-C₈ alkoxycarbonyl, hydroxyl, C₁-C₈ alkylcarbonyl, phenyl or phenoxy.

Particularly preferred are those compounds wherein R⁶ is

25



Z² is O or S;

30 R¹ is hydrogen; fluoro; or methyl;

R² is hydrogen, chloro, fluoro, or methyl;

R³ is hydrogen or methyl;

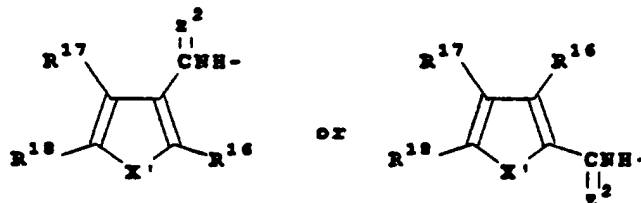
R⁴ is cyclopentyl or cyclohexyl;

R⁵ is hydrogen; and

35 R¹⁵ is methyl, ethyl or propyl.

Additionally preferred compounds are the furan, thiophene and pyrrole derivatives of the compound of formula I wherein R⁶ is:

5



10

Z² is O or S;

X¹ is O, S, NH or N-methyl,

R¹⁶ is hydrogen, methyl, ethyl,

1,1-dimethylethyl, fluoro, chloro, carboxyl, acetamido, cyano, C₁-C₆ alkylthio, C₁-C₆ haloalkoxy, C₁-C₆ acyloxy,

15

(C₁-C₆ alkoxy)carbonyl, or (C₁-C₆ alkyl)carbonyl; and

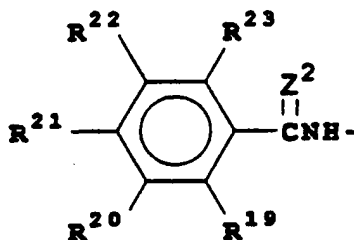
R¹⁷ and R¹⁸ are independently hydrogen or methyl.

More preferred furan, thiophene and pyrrole derivatives are those wherein R¹, R³ and R⁵ are hydrogen, R² is halogen, R⁴ is C₁-C₆ alkenyl or C₃-C₆ alkynyl, which can be linear, branched or cyclic, and Z² is S.

20

Also preferred are the compounds of formula I wherein R⁶ is:

25



30

Z² is O or S;

R¹⁹, R²⁰, R²¹, and R²² are independently hydrogen or halogen, preferably hydrogen; and

R²³ is hydrogen, halogen, C₁-C₄ alkyl, C₁-C₄ alkoxy, mono, di- or tri-haloalkoxy, C₁-C₄ hal alkyl, C₁-C₄ alkylthio, amino, C₁-C₆ alkylcarbonylamino, hydroxyl,

35

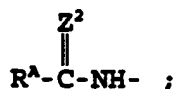
acetyl, acetyloxy, or acetylamino, preferably hydrogen, methyl, ethyl, chloro, iodo, amino, bromo, fluoro, methylthio, methoxy, difluoromethoxy, or hydroxy.

Also preferred as compounds of this invention are the derivatives of acyclic carboxamides or carbamates of the compound of formula I wherein X, Z², R¹, R², R³, R⁴ and R⁵ are as recited above for formula I and R⁶ is



wherein R^A is a linear or branched C₃-C₆ alkyl, C₃-C₆ alkenyl, C₁-C₆ alkoxy, C₃-C₆ alkenyloxy, C₃-C₆ alkynyloxy, C₃-C₆ mono- or di-alkylamino, or C₃-C₆ alkynyl; phenyl, C₇-C₈ phenylalkyl, C₇-C₈ phenoxyalkyl, C₃-C₇ cycloalkyl, or C₃-C₇ cycloalkenyl.

More preferred compounds are the compounds of formula I wherein R¹ is hydrogen or fluoro; R⁴ is C₃-C₆ alkenyl or C₃-C₆ alkynyl, which may be linear, branched or cyclic; R⁶ is



R^A is a linear or branched C₃-C₆ alkyl, C₃-C₆ alkenyl, C₃-C₆ alkynyl, C₃-C₆ alkoxy, C₃-C₆ alkenyloxy or C₃-C₆ alkynyloxy; C₇-C₈ phenylalkyl, C₇-C₈ phenoxyalkyl, C₃-C₆ cycloalkyl, or C₃-C₇ cycloalkenyl.

Especially preferred compounds of this invention are the compounds of formula I wherein R¹-R⁵ are hydrogen; R⁴ is C₃-C₆ alkenyl or C₃-C₆ alkynyl, which may be linear, branched or cyclic; R⁶ is



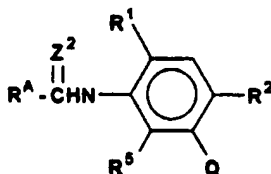
R^A is a linear or branched C₃-C₆ alkyl, C₃-C₆ alkoxy, C₃-C₆ alkenyloxy, C₃-C₆ alkynyloxy, C₃-C₆ cycloalkyl, or C₃-C₆ cycloalkenyl.

The compounds of this invention are useful for the inhibition of the growth or replication of retroviruses, particularly human immunodeficiency viruses such HIV-1, in vitro and in vivo. The compounds are useful in the therapeutic or prophylactic treatment of diseases caused by retroviruses, such as acquired immune deficiency syndrome or an HIV infection in a human or other mammal.

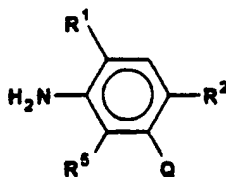
It is intended that the scope of this invention encompass all isomers, including positional or stereoisomers, of any compound of formula I exhibiting isomerism. It is also intended that any novel processes or intermediates for synthesizing said compounds be included within the scope of this invention.

GENERAL SYNTHETIC METHODS

Compounds of formula



wherein Z² is O and R³ is oxathiinyl, furanyl, thienyl, pyrrolyl, other heterocyclyl, or substituted phenyl, can be prepared from the appropriate carboxylic acid, R³-COOH, and an aniline derivative, i.e;



by employing one of the methods known in the art of amide bond formation. For example, the carboxylic acid can be converted to an acid halide, such as the acid chloride,

R^ACOCl, which can then be reacted with the aniline derivative to form the amide. The amide forming reaction is carried out in an appropriate solvent, such as methylene chloride, toluene, methyl ethyl ketone, tetrahydrofuran, dimethylformamide or acetonitrile, at a temperature of about 0°C to about 100°C.

It is usually preferable to carry out the reaction in the presence of a base, such as triethylamine or pyridine. Other reactive derivatives of the carboxylic acid can be employed: for example the anhydride of the carboxylic acid or a mixed anhydride, such as alkoxycarbonyloxy derivative, can be reacted with the aniline derivative. Alternatively, the carboxylic acid and aniline derivative can be reacted directly in the presence of a condensing agent such as dicyclohexylcarbodiimide to form the amide.

The aniline derivatives can be prepared by reduction of the corresponding nitro compounds by well-known methods, for example with hydrogen and a catalyst, such as Raney nickel or platinum, or with a metal-acid combination, such as iron or tin and hydrochloric or acetic acid. Oxime ethers are made from the corresponding aldehyde by conventional methods. An exception is in the preparation of tertiary o-alkyl oximes which are made by the action of an unsubstituted oxime and a tertiary alcoholic ester under acid catalysis in a suitable solvent such as THF, dioxane or DME. A suitable acid catalyst would be hydrochloric, sulphuric or perchloric acid.

Other compounds of this invention in which R^A is an alkoxy can be prepared by reacting the appropriate aniline derivative with an alkoxycarbonyl chloride, under conditions essentially similar to those used for reaction of an acid chloride with the aniline derivative. They can also be prepared by reacting the appropriate isocyanate derivative with an alcohol. The isocyanate can be

prepared by reacting the aniline derivative or a suitable salt thereof, such as the hydrochloride, with phosgene or a phosgene substitute, such as trichloromethyl chloroformate.

5 Compounds of this invention wherein R^A is alkoxy and Z^2 is sulphur can be similarly prepared using alkoxy thiocarbonyl chloride under conditions described above or from the appropriate isothiocyanate derivative and an alcohol.

10 Thiocarboxanilides of this invention wherein Z^2 is S and R^A is furanyl, thienyl, pyrrolyl, other heterocyclyl or substituted phenyl, can be prepared starting from the corresponding amide and reacting it with a sulfurating agent such as Lawesson's reagent or phosphorus
15 pentasulphide in a suitable solvent such as toluene, xylene, DME, pyridine, or the like.

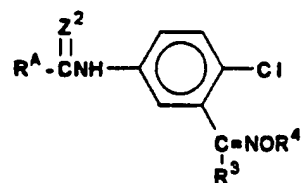
20 The following examples are provided to illustrate the synthesis of the compounds of the present invention.

Example I

25 The following Tables 1a and 1b list representative compounds that were prepared using the methods described above.

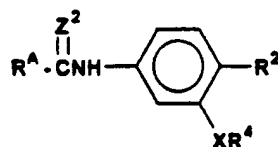
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TABLE 1a



| TABLE 1a | | | | | |
|----------|------------------------------|----------------|----------------|--|---------|
| No. | R ^A | Z ² | R ³ | R ⁴ | mp °C |
| 1 | 2-CH ₃ -3-Furanyl | O | H | CH ₂ C≡CH | 135-136 |
| 2 | " | S | H | CH ₂ CH=CH ₂ | 88-89 |
| 3 | " | S | H | CH ₂ CH=CH | 79-80 |
| 4 | " | S | H | CH ₂ C ₆ H ₅ | 131-133 |
| 5 | " | S | H | CH ₂ CO ₂ C(CH ₃) ₃ | 130-131 |
| 6 | " | S | H | C ₆ H ₅ (cyclo) | 73-75 |

TABLE 1b



| TABLE 1b | | | | | | |
|----------|-------------------------------------|----------------|---|----------------|--|---------|
| No. | R ^A | Z ² | X | R ³ | R ⁴ | mp °C |
| 7 | (CH ₃) ₃ CHO | S | O | Cl | CHF ₂ | 110-115 |
| 8 | " | S | O | Cl | COCH(CH ₃) ₂ | 89-91 |
| 9 | " | S | O | Cl | CH ₂ COCH ₃ | 104-106 |
| 10 | " | S | O | Cl | CH ₂ C(=NOH)CH ₃ | 101-105 |

IN VITRO SCREENING RESULTS

Representative compounds of this invention were tested for anti-viral activity by subjecting them to standard National Cancer Institute ("NCI") in vitro screening procedures. Two blanks were run with each test. The NCI test for agents active against HIV is designed to detect agents acting at any stage of the virus reproduction cycle.

In the test assay, small amounts of HIV are added to T4 lymphocyte cells. The assay measures the amount of T4 lymphocytes "killed" by HIV cytolysis. Since a complete cycle of viral reproduction is necessary to "kill" the T4 lymphocyte cells, agents that interfere with viral reproduction will protect the cells from cytolysis.

The NCI system is automated in several features to accomodate large numbers of candidate agents and is generally designed to detect anti-HIV activity. Compounds that degenerate or are rapidly metabolized in the culture conditions do not show activity in this screen. All tests are compared with at least one positive (AZT-treated) control done at the same time under identical conditions.

The Test Procedure

1) The test compound was dissolved in dimethyl sulfoxide and diluted 1:100 in cell culture medium before serial half-log₁₀ dilutions were prepared. T4 lymphocytes (CEM cell line) were then added to the cell culture medium, and, finally, after a brief interval, HIV-1 was added, resulting in a 1:200 final dilution of the test compound. Uninfected cells in the cell culture medium containing the test compound (i.e., minus HIV-1) were used as a toxicity control, and infected cells in the cell culture medium without the test compound and uninfected

cells in the cell culture medium without the test compound, were used as basic controls.

5 2) The cultures were incubated at 37°C in a 5% carbon dioxide atmosphere for 6 days.

10 3) The tetrazolium salt, XTT, was added to all wells, and the cultures were then incubated to allow formazan color development by viable cells.

15 4) Individual wells were analyzed spectrophotometrically to quantitate formazan production, and were also viewed microscopically for detection of viable cells and confirmation of protective activity.

20 5) Virus-infected cells exposed to the test compound were compared with noninfected cells exposed to the test compound, and with other appropriate controls (infected cells not exposed to the test compound and noninfected cells not exposed to the test compound, wells containing only the test compound in the cell culture medium, and so on) on the same plate. These are the first and second blanks described below.

25 6) Data were reviewed in comparison with other tests done at the same time and a determination concerning activity was made. In the first blank, HIV and T4 lymphocytes in cell culture medium, were incubated together to measure the infectivity of the virus. The viability of the cells was measured after holding for six or seven days. In an "effective" test, most cells were infected before the holding period was complete.

30 In the second blank, the T4 lymphocytes in cell culture medium and the test compound (with no HIV-1) were incubated together to measure the toxicity of the drug to the cells. The viability of the cells was measured as

a function of concentration of the compound, after incubation for seven days. The concentration of the test compound that results in 50% inhibition of cell growth is defined as its IC_{50} .

5 Finally, the protective effects of the test compounds were measured. Each cell culture and test compound were incubated with the virus and the viability of the cells was measured as a function of compound concentration after incubation for six or seven days.

10 The concentration of the test compound that results in 50% "control," i.e., a 50% reduction of the viral cytopathic effect, is defined as its EC_{50} . The therapeutic index TI_{50} was calculated as IC_{50}/EC_{50} .

15 Concentrations of test compounds required for between 20 and 50% reduction of the viral cytopathic effect can also be determined. Such compounds are classified as moderately active. Compounds with less than 20% control are considered inactive.

20 The compounds were tested to determine their reduction of HIV cytopathic effect on the human cell line CEM. Tests were done by innoculating these cell lines in-well (IW), i.e., the test compound and CEM cells were mixed on a test plate and the virus was added a short time later.

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Screening Data for Test Compound Exhibiting Inhibition of HIV

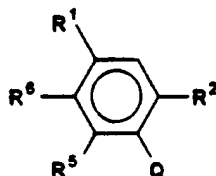
30 The preceding protocol was carried out with all of the compounds described above in the Examples, all of which showed some significant activity in at least one of the tests. The test results (molar) for all the tested compounds are shown in Table 2 as IC_{50} , EC_{50} and TI_{50} .

TABLE 2

| Compound | IC ₅₀ (M) | EC ₅₀ (M) | TL ₅₀ |
|----------|----------------------|----------------------|------------------|
| 1 | 1.80×10^5 | 3.30×10^4 | 5 |
| | 1.80×10^5 | 3.50×10^4 | 5 |
| | $>2.30 \times 10^5$ | 3.90×10^4 | >6 |
| | $>2.30 \times 10^5$ | 3.70×10^4 | >6 |
| 2 | $>1.80 \times 10^5$ | 1.10×10^3 | >1400 |
| | $>1.80 \times 10^5$ | 2.00×10^3 | >770 |
| | $>1.80 \times 10^5$ | 4.50×10^3 | >340 |
| | $>1.80 \times 10^5$ | 1.20×10^3 | >1300 |
| 3 | 1.80×10^5 | 4.70×10^3 | 340 |
| | 1.80×10^5 | 3.80×10^3 | 440 |
| | $>2.20 \times 10^5$ | 1.30×10^7 | >170 |
| | 2.10×10^5 | 1.10×10^7 | 180 |
| 4 | $>7.10 \times 10^5$ | 1.00×10^4 | >7 |
| | $>7.10 \times 10^5$ | 1.80×10^4 | >4 |
| | $>7.10 \times 10^5$ | 1.30×10^4 | >5 |
| | $>7.10 \times 10^5$ | 1.10×10^4 | >7 |
| 5 | $>2.40 \times 10^5$ | 2.00×10^4 | >1 |
| | $>2.40 \times 10^5$ | - | - |
| | 1.90×10^5 | 4.40×10^4 | 4 |
| | 2.30×10^5 | - | - |
| 6 | $>1.40 \times 10^5$ | 2.50×10^7 | >58 |
| | $>1.40 \times 10^5$ | 2.40×10^7 | >58 |
| | $>1.40 \times 10^5$ | 1.80×10^7 | >78 |
| | $>1.40 \times 10^5$ | 8.40×10^6 | >170 |
| 7 | 3.47×10^5 | 2.82×10^4 | 13 |
| | 4.84×10^5 | 8.37×10^4 | 6 |
| | 3.22×10^5 | - | - |
| | 3.33×10^5 | 5.78×10^4 | 6 |
| 8 | 5.58×10^5 | - | - |
| | 5.13×10^5 | 2.90×10^5 | 2 |
| | 4.17×10^5 | 2.54×10^5 | 2 |
| | 4.75×10^5 | 1.81×10^5 | 3 |
| 9 | 7.70×10^5 | 2.70×10^4 | 28 |
| | $>1.20 \times 10^6$ | 2.80×10^4 | >61 |
| | $>1.20 \times 10^6$ | 4.80×10^4 | >28 |
| | $>1.20 \times 10^6$ | 1.10×10^5 | >110 |
| | 1.20×10^6 | 3.30×10^4 | 36 |
| 10 | - | 9.7×10^5 | - |
| | - | 8.8×10^5 | - |
| | - | 2.0×10^7 | - |
| | - | 1.8×10^7 | - |

What is claim d is:

1. A compound of the formula



wherein Q is -C=NOR^4 or -XR^5 ;

5



X is oxygen or sulphur;

R¹ is hydrogen, halogen, C₁-C₄ alkyl or C₁-C₄ alkoxy;

R² is hydrogen, halogen, C₁-C₄ alkyl, C₁-C₄ alkoxy, C₃-C₆ alkenyloxy, C₃-C₆ alkynyloxy, mono-, di- or tri-halomethyl, trifluoromethoxy, C₁-C₄ alkylthio, C₃-C₆ branched alkylthio, nitro, or cyano;

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R³ is hydrogen or C₁-C₄ alkyl;

R⁴ is C₃-C₆ alkenyl, C₃-C₆ alkynyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxyalkyl, C₁-C₆ alkylthioalkyl, C₁-C₆ hydroxyalkyl, C₁-C₆ acyloxyalkyl, C₁-C₆ aryloxyalkyl, C₁-C₆ carboxyalkyl, C₁-C₆ alkylcarboxyalkyl, C₆-C₁₂ arylcarboxyalkyl, C₁-C₆ aminoalkyl, C₁-C₆ alkylaminoalkyl, C₁-C₆ dialkylaminoalkyl, C₁-C₆ trialkylsilylalkyl, wherein each of the aforementioned alkyl moieties may be straight-chain or branched; C₃-C₆ cycloalkyl, C₁-C₆ alkylphenyl, C₇-C₁₂ arylalkyl, C₇-C₁₂ alkarylalkyl, or heterocyclalkyl, wherein the heterocyclic moiety is morpholinyl, piperidinyl, pyrrolidinyl, piperazinyl, oxiranyl, oxetanyl, furanyl, tetrahydropyranyl or tetrahydrofuranyl;

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R⁵ is C₁-C₆ haloalkyl, C₁-C₆ alkoxyalkyl, C₁-C₆ alkylthioalkyl, C₁-C₆ hydroxyalkyl, C₁-C₆ acyloxyalkyl, C₁-C₆ aryloxyalkyl, C₁-C₆ aminoalkyl, C₁-C₆ alkylaminoalkyl, C₁-C₆ dialkylaminoalkyl, C₁-C₆ trialkylsilylalkyl, where in each of the aforementioned

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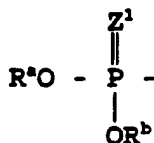
alkyl moieties may be straight-chain or branched; C₁-C₆, alkylphenyl, C₇-C₁₂, arylalkyl, C₇-C₁₂, alkarylalkyl, or heterocyclalkyl, wherein the heterocyclic moiety is morpholinyl, piperidinyl, pyrrolidinyl, piperazinyl, oxiranyl, oxetanyl, furanyl, tetrahydropyranyl or tetrahydrofuranyl;

R⁵ is hydrogen, halo, methyl, mono-, di- or tri-halomethyl; and

R⁶ is

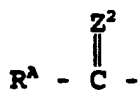
1) R² - NH -, wherein R² is

A)



wherein R^a and R^b are independently hydrogen or C₁-C₆ alkyl; and Z¹ is O or S;

B)



wherein Z² is O or S; and R^a is:

a) fully unsaturated, partially or fully reduced or substituted oxathiinyl, furanyl, dithiinyl, dioxinyl, thienyl, thiazolyl, oxazolyl, isoxazolyl, isothiazolyl, thiadiazolyl, pyrazolyl, pyrrolyl, imidazolyl, pyranyl, oxathiazinyl, oxadiazolyl, or indolyl;

b) substituted or unsubstituted, linear or branched C₁-C₆ alkyl, C₃-C₆ alkenyl, C₃-C₆ alkynyl, C₁-C₆ alkoxy, C₃-C₆ alkenyloxy, C₃-C₆ alkynyloxy, or C₁-C₆ mono- or di-alkylamino; C₃-C₆ cycloalkyl, C₃-C₆

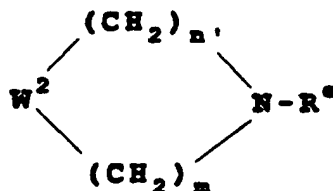
cycloalkyloxy, C₃-C₆ cycloalkylalkoxy, C₃-C₆ cycloalkyl C₁-C₆ alkyl, C₃-C₆ cycloalkenyl, unsubstituted or substituted by C₁-C₆ alkyl or C₇-C₈ phenylalkyl; or

- 5 c) aryl, aralkyl, aryloxyalkyl, or cycloalkylaryloxy wherein each alkyl moiety contains from 1 to 10 carbon atoms and each aryl moiety is naphthyl, phenyl or phenyl substituted by one or more halo,
- 10 C₁-C₆ alkyl, carboxyl, C₁-C₆ haloalkyl, C₁-C₆ alkylthio, phenyl, nitro, amino, C₁-C₆ alkoxy-carbonylamino, hydroxyl, acetyl, acetyloxy, phenoxy, C₁-C₆ alkoxy-carbonyl or C₁-C₆ alkyl-carbonyl:
- 15 (d) R' - W -, wherein W is O, NH or NR^f wherein R^f is C₁-C₆ alkyl; and R' is linear or branched, unsubstituted or halo-substituted C₁-C₆ alkyl, C₃-C₆ alkenyl, C₃-C₆ alkynyl, C₃-C₆ cycloalkyl C₁-C₆ alkyl, C₃-C₆ cycloalkenyl unsubstituted or
- 20 substituted by C₁-C₆ alkyl, unsubstituted phenyl or phenyl substituted by halo, C₁-C₆ alkyl, C₁-C₆ alkoxy, carboxyl, C₁-C₆ alkythio, phenyl, nitro, amino, hydroxyl,
- 25 acetyl, acetyloxy, phenoxy, C₁-C₆ alkoxy-carbonyl, or C₁-C₆ alkyl-carbonyl; furanylalkyl, tetrahydrofuranylalkyl, oxetanylalkyl, or oxiranylalkyl;
- 30 e) R^g - W¹ - R^h, wherein R^h is a linear or a branched C₁-C₆ alkylidene; W¹ is O or S; and R^g is linear or branched C₁-C₆ alkyl;

- f) $R^9 R^{10} - N - R^*$, wherein
 R^* is as defined above; and R^9 and R^{10} are
independently linear or branched C_1-C_4
alkyl;

5

g)



wherein

- R^* is as defined above;
 W^2 is O, S, NH, NR^{11} or $CR^{12}R^{13}$; wherein R^{11}
is linear or branched C_1-C_4 alkyl; R^{12} and
 R^{13} are independently hydrogen or linear or
branched C_1-C_4 alkyl; and
 n' and m are independently 1, 2 or 3;

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- h) $R^{14}-O_2-C-R^*$,

wherein

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- R^* is as defined above; and R^{14} is linear
or branched C_1-C_6 alkyl, C_3-C_6 alkenyl, or
 C_3-C_6 alkynyl; or C_3-C_6 cycloalkyl, C_3-C_6
cycloalkyl C_1-C_6 alkyl, or C_3-C_6
cycloalkenyl, unsubstituted or substituted
by C_1-C_6 alkyl;

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- i) $U-R^*$ -, wherein
 R^* is as defined above; U is hydroxyl,
acyloxy, aryloxy, arylsulphonyloxy, nitro,
cyano or trimethylsilyl;

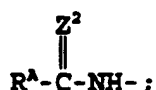
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- j) 1-adamantyl, 2-adamantyl or bornyl;

- k) $Ar^1 - R^*$ -, wher in

R^o is as defined above; and
 Ar¹ is phenyl or phenyl substituted
 independently with one to three halogen,
 mono-, di- or tri- halomethyl, nitro, C₁-C₄
 alkyl, C₁-C₄ alkenyl, C₁-C₄ alkyloxy, C₁-C₄
 alkenyloxy, or C₁-C₄ alkynyloxy.

2. A compound as recited in claim 1 wherein R⁶ is



Z² is O or S; and

R^A is

a) fully unsaturated, partially or fully reduced or
 substituted oxathiinyl, furanyl, dithiinyl, dioxinyl,
 thienyl, thiazoyl, oxazoyl, isoxazoyl, isothiazoyl,
 thiadiazolyl, pyrazolyl, pyrrolyl, pyranyl, oxathiazinyl,
 or oxadiazolyl;

b) linear or branched C₁-C₈ alkyl, C₁-C₈ alkenyl, C₁-C₈
 alkynyl, C₁-C₈ alkoxy, C₁-C₈ alkenyloxy,
 C₁-C₈ alkynyloxy, or C₁-C₈ mono- or di- alkylamino; C₁-C₈
 cycloalkyl or C₁-C₈ cycloalkenyl;

c) phenyl or phenyl substituted by one or more halo,
 C₁-C₈ alkyl, C₁-C₈ haloalkyl, C₁-C₈ alkylthio, phenyl,
 amino, hydroxyl, carboxyl, acetyl, acetyloxy, C₁-C₈
 alkoxycarbonyl, C₁-C₈ alkylcarbonyl or phenoxy; C₁-C₈
 phenylalkyl or C₁-C₈ phenoxyalkyl.

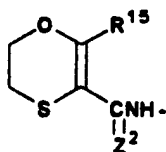
3. A compound as recited in claim 2 wherein R^A is

a) dihydro-3-oxathiinyl, furanyl, dihydrofuranyl,
 thienyl, pyrrolyl, dihydro-2-dithiinyl, or
 dihydro-2-dioxinyl, which can be substituted by one to
 three C₁-C₄ alkyl or C₁-C₄ alkoxyalkyl groups;

b) linear or branched C₁-C₈ alkyl, C₁-C₈ alkenyl,
 C₁-C₈ alkynyl, C₁-C₈ alk xy, C₁-C₈ mono- or di-alkylamino,
 C₁-C₈ cycloalkyl or C₁-C₈ cycloalk nyl; r

c) phenyl or phenyl substituted by one or more halo, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkylthio, carboxyl, amino, C₁-C₆ alkoxy, carbonyl, hydroxyl, C₁-C₆ alkylcarbonyl, phenyl or phenoxy.

5 4. A compound as recited in claim 3 wherein R⁶ is



Z² is O or S;

R¹ is hydrogen; fluoro; or methyl;

R² is hydrogen, chloro, fluoro, or methyl;

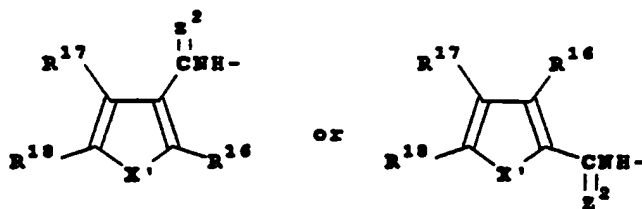
R³ is hydrogen or methyl;

10 R⁴ is cyclopentyl or cyclohexyl;

R⁵ is hydrogen; and

R¹⁵ is methyl, ethyl or propyl.

5. A compound as recited in claim 2 wherein R⁶ is:



Z² is O or S;

15 X¹ is O or S or N-methyl,

R¹⁶ is hydrogen, methyl, ethyl,

1,1-dimethylethyl, fluoro, chloro, carboxyl, acetamido, cyano, C₁-C₆ alkylthio, C₁-C₆ haloalkoxy, C₁-C₆ acyloxy, (C₁-C₆ alkoxy)carbonyl, or (C₁-C₆ alkyl)carbonyl; and

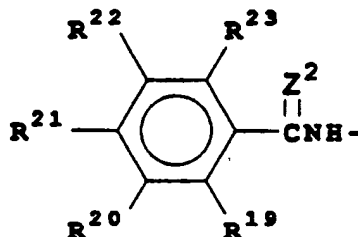
20 R¹⁷ and R¹⁸ are independently hydrogen or methyl.

6. A compound as recited in claim 5 wherein R¹, R³

and R^5 are hydrogen, R^2 is halogen, R^4 is C_3 - C_6 alkenyl or C_3 - C_6 alkynyl, which can be linear, branched or cyclic, and R^{16} is hydrogen, methyl, ethyl or 1,1-dimethylethyl.

7. A compound as recited in claim 2 wherein R^6 is:

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Z^2 is O or S;

R^{19} , R^{20} , R^{21} , and R^{22} are independently hydrogen or halogen; and

10 R^{23} is hydrogen, halogen, C_1 - C_4 alkyl, C_1 - C_4 alkoxy, mono, di- or tri-haloalkoxy, C_1 - C_4 haloalkyl, C_1 - C_4 alkylthio, amino, C_1 - C_4 alkylcarbonylamino, hydroxyl, acetyl, acetyloxy, or acetylamino.

15 8. A compound as recited in claim 2 wherein R^A is a linear or branched C_3 - C_6 alkyl, C_3 - C_6 alkenyl, C_3 - C_6 alkynyl, C_3 - C_6 alkoxy, or C_3 - C_6 mono- or di-alkylamino; phenyl, C_7 - C_8 phenylalkyl, C_7 - C_8 phenoxyalkyl, C_3 - C_7 cycloalkyl, or C_3 - C_7 cycloalkenyl.

20 9. A compound as recited in Claim 2 wherein Q is $-CR^3=NOR^4$, R^A is C_1 - C_4 alkoxy, phenyl, or dihydro-3-oxathiinyl, furanyl, dihydrofuranyl or thienyl substituted by one to three methyl or ethyl groups, R^1 is H, R^2 is Cl, R^3 is H or methyl, R^4 is C_3 - C_6 carboxyalkyl or C_5 - C_7 cycloalkyl, and R^5 is H.

10. A compound as recited in Claim 9 wherein R^A is

C₁-C₆ alkoxy, Z² is S, and R³ is H.

11. A compound as recited in claim 9 wherein R^A is 2-methyl-3-furanyl, Z² is S, and R³ is H.

5 12. A compound as recited in claim 2 wherein Q is -XR', R^A is C₁-C₆ alkoxy, phenyl, or furanyl, thienyl or dihydro-3-oxathiinyl substituted by one to three methyl or ethyl groups; R² is Cl or methoxy; and R' is C₁-C₆ dihaloalkyl or C₁-C₆ alkoxyalkyl.

10 13. A method for inhibiting the growth or replication of a retrovirus in a patient infected by the retrovirus which comprises administering to the patient an effective amount of a compound as recited in claim 1.

15 14. A method as recited in claim 18 wherein the retrovirus is a HIV.

15 15. A method for inhibiting the growth or replication of a retrovirus in a patient infected by the retrovirus which comprises administering to the patient an effective amount of a compound as recited in claim 2.

20 16. A method as recited in claim 20 wherein the retrovirus is a HIV.

25 17. A method for therapeutically or prophylactically treating a retroviral infection in a patient, which comprises administering to the patient a therapeutically or prophylactically effective amount of a compound as recited in claim 1.

18. A method as recited in claim 22 wherein the retrovirus is a HIV.

19. A method for therapeutically or prophylactically treating a retroviral infection in a patient, which comprises administering to the patient a therapeutically or prophylactically effective amount of a
5 compound as recited in claim 2.

20. A method as recited in claim 24 wherein the retrovirus is a HIV.